Full title

Processes underlying glycemic deterioration in type 2 diabetes: An IMI DIRECT study

Running title

Glycemic deterioration in type 2 diabetes

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Abstract

Objective

We investigated the processes underlying glycemic deterioration in type 2 diabetes (T2D).

Research Design and Methods

732 recently diagnosed T2D patients from the IMI-DIRECT study were extensively phenotyped over three years, including measures of insulin sensitivity (OGIS), β-cell glucose sensitivity (GS) and insulin clearance (CLIm) from mixed meal tests, liver enzymes, lipid profiles, and baseline regional fat from MRI. The associations between the longitudinal metabolic patterns and HbA_{1c} deterioration, adjusted for changes in BMI and in diabetes medications, were assessed via stepwise multivariable linear and logistic regression.

Results

Faster HbA_{1c} progression was independently associated with faster deterioration of OGIS and GS, and increasing CLIm; visceral or liver fat, HDL-cholesterol and triglycerides had further independent, though weaker, roles (R^2=0.38). A subgroup of patients with a markedly higher progression rate (fast progressors) was clearly distinguishable considering these variables only (discrimination capacity from AUROC=0.94). The proportion of fast progressors was reduced from 56% to 8-10% in subgroups in which only one trait among OGIS, GS and CLIm was relatively stable (odds ratios 0.07 to 0.09). T2D polygenic risk score and baseline pancreatic fat, GLP-1, glucagon, diet, and physical activity did not show an independent role.

Conclusions

Deteriorating insulin sensitivity and β-cell function, increasing insulin clearance, high visceral or liver fat, and worsening of the lipid profile are the crucial factors mediating glycemic deterioration

of T2D patients in the initial phase of the disease. Stabilization of a single trait among insulin sensitivity, β-cell function, and insulin clearance may be relevant to prevent progression.

Maintaining glucose levels within appropriate limits in patients with type 2 diabetes (T2D) is a crucial factor to prevent complications. Effective strategies to slow glycemic progression can be supported by understanding the processes underlying deterioration of glucose control.

Few studies have assessed HbA_{1c} trajectories and the possible determinants of glycemic deterioration. An established finding is that β-cell function decline is an important factor (1,2), while contradictory conclusions were drawn for insulin sensitivity (1,3–7). Whether heterogeneous patterns between patients exist in β-cell function and insulin sensitivity decline has not been clarified, an important question for patient stratification and personalized medicine. Other limitations of previous analyses include the incomplete characterization of the metabolic parameters affecting glucose homeostasis (derived using fasting data only (2,4)), the restricted set of traits investigated together, and the lack of potentially relevant measures such as ectopic fat, insulin clearance, or lifestyle. No study has assessed the relationships between the longitudinal trajectories of HbA_{1c} and those of the other metabolic traits.

In this analysis, we have used data from the cohort of recently diagnosed and extensively phenotyped T2D patients of the DIRECT study (8,9) to elucidate the processes underlying glycemic deterioration. Specific features of the DIRECT study are the detailed assessment of the glucose homeostasis parameters, and patients all being in the initial phase of the disease. We determined the patterns over a 3-year period of HbA_{1c}, β-cell function, insulin sensitivity and other relevant laboratory, clinical and functional parameters, and assessed their relevance in the deterioration of glucose control.

Research Design and Methods

Subjects and protocol

The IMI-DIRECT (Innovative Medicines Initiative - Diabetes Research on Patient Stratification) project is a multicenter prospective study on northern European adults (8,9) (ClinicalTrials.gov

identifier NCT03814915). The present analysis considers the DIRECT cohort of recently diagnosed T2D patients, who were recruited according to the following criteria: white race, T2D diagnosis according to the American Diabetes Association 2011 criteria (10) not less than 6 months and not more than 24 months before baseline examination, previous treatment via lifestyle measures with or without metformin therapy, age between 35 and 74 years, BMI between 20 and 50 kg/m^2, estimated glomerular filtration rate >50 ml/min, and HbA_{1c} concentration <7.64 % (60.0 mmol/mol) within the previous 3 months. Participants were studied at baseline (month 0) and at months 9, 18 and 36. Subjects with HbA_{1c} available at least in two visits were included in this analysis (*N*=750).

All participants provided written informed consent and the study protocol was approved by the regional research ethics review boards. The research conformed to the ethical principles for medical research involving human participants outlined in the declaration of Helsinki.

Collected data

Anthropometric data, HbA_{1c}, blood lipids and liver enzymes were collected at all visits. A 27-month HbA_{1c} sample was collected in 39 patients. A standardized mixed meal test (8) (MMTT) was performed at months 0, 18 and 36 to calculate indices of insulin sensitivity (in fasting conditions, QUICKI (11), and post-MMTT, OGIS (12)), β-cell function (13) (glucose sensitivity, GS, and rate sensitivity), and insulin clearance (in fasting conditions, and post-MMTT, CLIm). From the baseline visit we collected glucagon, proinsulin and glucagon-like peptide 1 (GLP-1), measures of regional fat from MRI (8) (available in 561 participants), of physical activity from accelerometer (8), and of self-reported 24-hour nutrient intake (8), and we computed the fatty liver index (FLI) (14) and a T2D polygenic risk score (PRS) (15). The whole set of traits considered in this study is described in detail in the Supplemental Material (DATA, METHODS, and Table S2).

Assessment of progression rates

We computed the progression rates for HbA_{1c} and several traits available at follow up (Supplemental Table S4). Each trajectory was described with a conditional linear mixed-effect model (16), in which the longitudinal component of the data was described as a proportional function of time, with normally distributed slopes describing individual progression rates. HbA_{1c} progression was adjusted for changes in BMI and diabetes medications, which were recorded at all visits (as dosage and start and end of treatment). The adjustments were assumed to be 1) proportional to BMI; 2) linearly related to the metformin dose, expressed as percentage of a maximal dose of 3 grams; 3) linearly related to the cumulative dose for the other antidiabetic drugs (insulin excluded), expressed as sum of the percentages of the maximum dose of each drug; 4) constant under insulin treatment. A proportional effect of delay in HbA_{1c} assay, i.e. of the difference between the time of measurement and the time of sample collection, was also introduced. Medications were considered to be effective if taken at least 30 days before HbA1c measurement. OGIS and QUICKI trajectories were adjusted for changes in BMI. Further details about the conditional linear mixed-effect models are provided in the Supplemental Material (METHODS).

Statistical analysis

Results are presented for participants (N=732) with GAD <11 U/ml and islet antigen-2 antibodies (IA-2) <7.5 U/ml, to exclude other possible forms of diabetes (17). Distributions are described as mean ± standard deviation. Pairwise associations between continuous variables were assessed using the Spearman correlation coefficient; differences between groups were assessed using the Wilcoxon signed rank test (for two groups) and Kruskal-Wallis test (for three or more groups).

We used stepwise multivariable linear regression to determine the set of variables, as baseline values (Table S2) and progression rates (Table S4), independently associated with the HbA_{1c} progression rate, with adjustment for center, sex and age. For baseline variables, both untransformed and transformed values were considered; transformations were logarithmic, or logit when variables where constrained within an interval. The independent variables were included in

the regression model when their effects had $p<0.05$ and produced an increment in the adjusted R^2 value. Two stepwise analyses were performed: one on all participants, excluding MRI variables from the analysis, and one on the subset of participants with MRI data, including this data in the analysis. Standardized coefficients were computed per standard deviation of the underlying data distribution.

Since the distribution of HbA_{1c} progression rates was skewed to the right with a group of patients with high values, we split the subjects into *average* and *fast* progressors according to a progression rate threshold (see Results). We used multivariable logistic regression to assess the odds ratios of average *vs* fast progression, using the independent variables identified in the multiple linear regression analysis of HbA_{1c} progression. The logistic analysis provided values for AUROC, sensitivity, specificity and accuracy, to be used as measures of the discrimination capacity of the investigated independent variables over fast *vs* average progressors. These parameters must not be interpreted as measures of predictive capacity.

Role of the funding source

The funders had no role in study design, in collection, analysis, and interpretation of data, in writing of the report, or in the decision to submit the paper for publication. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Subjects' baseline characteristics

At baseline, the participants had age of 62±8 years, were moderately obese (30.4±4.9 kg/m^2 BMI), and had HbA_{1c} of 6.41±0.53 % (46.5±5.8 mmol/mol) and fasting glucose of 7.1±1.4 mmol/l. (Table S2). 34% of the subjects were treated with metformin at baseline, the rest was treatment naïve.

Progression rates of HbA_{1c} and other traits

The individual HbA_{1c} progression rates (Supplemental Figure S1), adjusted for changes in BMI and in diabetes medications, were on average only slightly positive and mostly distributed close to their median (median, first and ninth deciles were 0.041, -0.038 and 0.185 %/year (0.45, -0.41 and 2.02 mmol mol^{-1} $year^{-1}$), respectively). However, the distribution showed a heavy right tail with values up to 0.897 %/year (9.8 mmol mol^{-1} $year^{-1}$). The adjustment of progression rates for BMI changes implied a standardized coefficient for the BMI effect of 0.37.

All the other investigated traits had a mean progression rate per year smaller, in absolute value, than 5% of the corresponding baseline average (see Table S5 for details). On average, waist circumference, but not BMI, increased very slightly. Insulin sensitivity (as OGIS) and most of the β-cell function parameters decreased. Fasting, but not post-meal, insulin clearance decreased. Total cholesterol did not change, while its fractions showed opposite changes, with HDL increasing and LDL decreasing; TG increased. Creatinine and ALT did not change, while AST and AST/ALT increased.

Several pairwise associations were observed between HbA_{1c} progression rate and laboratory, clinical, and functional parameters (Supplemental Figure S2). In particular, HbA_{1c} progression rate was clearly associated ($p<0.01$) with some baseline traits (positively with BMI, waist circumference, triglycerides, glucagon, liver and visceral fat; inversely with age, HDL, insulin sensitivity, and β-cell function) and some progression rates (positively with those of triglycerides and liver enzymes; inversely with those of insulin sensitivity, β-cell function, AST/ALT ratio, and HDL).

Several pairwise associations were also observed between the progression rates of the investigated traits (Figure S2, panel B). GS and OGIS progression rates were independent of one another despite HbA_{1c} progression rate being associated with both of them.

Variables associated with HbA_{1c} progression rate: multivariable linear analysis

In multivariable linear analysis of HbA_{1c} progression rate in all patients, the baseline values and the progression rates of several traits provided an independent contribution (adjusted R^2 0.38; Figure 1, panel A). Faster HbA_{1c} progression was independently associated with lower baseline values and faster deterioration of insulin sensitivity (as OGIS) and β-cell function (mostly as glucose sensitivity, GS), with higher baseline values of MMTT insulin clearance, CLIm, and with its increase (all p-values <0.001). Faster HbA_{1c} progression was also independently associated with lower baseline HDL (p<0.05) or its slower increase (p<0.001), with a quicker increase of TG (p<0.001), as well as with higher baseline values of BMI (p<0.01) and lower baseline values of HbA_{1c} (p<0.001). The variables with strongest effects were the baseline OGIS value and the progression rates of OGIS, GS and CLIm (standardized coefficients, in absolute value, between 0.24 and 0.57).

In multivariable analysis of the subset of patients with baseline MRI measurements (adjusted R^2 0.40; Figure 1, panel B), baseline visceral fat was positively and independently correlated with HbA_{1c} progression rate; moreover, female sex and younger age independently predicted faster HbA_{1c} progression. The role of the other key metabolic parameters, OGIS, GS and CLIm, remained similar. Replacing visceral fat with liver fat produced similar results (standardized coefficient equal to 0.15 for visceral fat, to 0.11 for liver fat); when both visceral and liver fat were included in the model, the latter was not independently associated with HbA_{1c} progression.

No independent effects were detected for smoking status, family history, T2D polygenic risk score, baseline values of diet, physical activity, pancreatic fat, GLP-1 (total and intact at fasting, total at 60 min), glucagon, and 60-min proinsulin, baseline values and progression rates of AST and ALT.

Further details on the multivariable linear analysis are reported in the Supplemental Material (RESULTS).

Variables associated with HbA_{1c} progression rate: multivariable logistic analysis

The threshold selected to separate the heavy right tail of the distribution of HbA_{1c} progression rates was 0.255 %/year (2.79 mmol mol^{-1} $year^{-1}$). This threshold split the subjects into average progressors (*N*=699), with a progression rate of 0.044±0.076 %/year (0.48±0.83 mmol mol^{-1} $year^{-1}$), and fast progressors (*N*=33), with a ~10-fold mean progression rate (0.460±0.185 %/year, 5.03±2.02 mmol mol^{-1} $year^{-1}$) (Figure 2).

We found that the trajectories of most variables independently affecting HbA_{1c} progression as from the linear analysis were clearly different ($p<0.001$) in the two groups (Figure 2): in fast progressors, OGIS and GS strongly declined and TG and CLIm markedly increased. At baseline, fast progressors had lower OGIS ($p<0.05$), CLIm ($p<0.01$) and HDL ($p<0.001$), and higher BMI ($p<0.01$).

Logistic analysis substantially confirmed the results of linear regression (Figure 1), with half the investigated variables still contributing ($p<0.05$) to distinguish average and fast progressors (Figure 3): fast HbA_{1c} progression independently associated with stronger deterioration and a lower baseline value of OGIS and GS, CLIm increase, and HDL reduction. The discrimination capacity of the logistic model, computed as AUROC, was 0.94 (95% CI between 0.86 and 0.98).

Similar outcomes were obtained using lower HbA_{1c} progression rate thresholds, which resulted in larger numbers of patients classified as fast progressors (Supplemental Material - RESULTS, Figures S1 and S3).

At baseline, the percentage of patients treated with metformin were not different between fast progressors (39.4% [24.7-56.3%, 95% CI]) and average progressors (33.9% [30.5-37.5%], p = 0.64). At the last visit, the percentage of patients treated with any diabetes medication was somewhat higher in fast progressors, as expected ($p = 0.048$, details provided in the Supplemental Material - RESULTS). Only 7 average progressors were on insulin at the last visit.

Impact of stable OGIS, GS or CLIm on proportion of fast HbA_{1c} progressors

Because HbA_{1c} progression was associated with worsening of three main factors, OGIS, GS and CLIm, we have evaluated the possible importance of maintaining one of these key traits relatively stable in order to avoid fast progression. For this purpose, we considered each trait as deteriorating if its progression rate fell within its worst tertile (the bottom tertile for OGIS and GS, the top one for CLIm), and as stable if it fell in the other two tertiles. We examined the subgroups of patients in which none or only one of these key traits was relatively stable (Table 1).

We found that the proportion of fast progressors was 56% in the patient subgroup where GS, OGIS and CLIm were all deteriorating, and decreased to 8-10% in the subgroups where a single trait, either GS, OGIS or CLIm, was stable. All proportions were different from 0 at 90% confidence level, stressing that fast progression did not imply quick changes for each of the three considered traits. All differences in proportions (one stable trait *vs* none) had $p<0.001$, and were associated to odds ratio for fast *vs* average progression below 0.1 (Table 1); thus, relatively stable progression rate of one single trait among GS, OGIS and CLIm was strongly associated to reduced glycemic deterioration.

Conclusions

Leveraging on the detailed participant characterization of the DIRECT study, we have been able to elucidate the processes underlying glycemic deterioration in T2D patients in the initial phase of the disease. We found that HbA_{1c} deterioration was independently associated with 1) a decrease in insulin sensitivity; 2) a decrease in β-cell function (primarily β-cell glucose sensitivity); 3) an increase in insulin clearance; 4) lower values of insulin sensitivity and glucose sensitivity and higher values of insulin clearance at baseline. Further variables independently associated with faster HbA_{1c} progression were declining HDL, increasing TG and high baseline visceral or liver fat.

The variables identified by multivariable linear analysis also explained the rapid HbA_{1c} deterioration detected in a subset of patients (identified as fast progressors), the strongest predicting variables of the multivariable linear model being significant also with logistic analysis. Clear

differences were evident between fast and average HbA_{1c} progressors (Figure 2), consistent with the associations derived from the multivariable linear analysis. The high discrimination capacity of the logistic analysis suggests that the selected variables capture the most relevant pathophysiological factors underlying glycemic deterioration.

The independent associations with HbA_{1c} progression of several variables, in particular the progression rates of insulin sensitivity, β-cell function and insulin clearance, and the existence of fast HbA_{1c} progressors with relatively stable conditions for any of these three traits (Table 1), indicates 1) that the processes of glycemic deterioration are heterogeneous in this population of T2D patients; 2) that fast progression does not imply quick deterioration of a specific trait, e.g. insulin sensitivity or β-cell function.

The dichotomous analysis shows that the odds for fast *vs* average progression are substantially reduced when either glucose sensitivity, insulin sensitivity or insulin clearance is relatively stable. Although these findings do not demonstrate causality, they suggest that preventing either high degradation rates of glucose sensitivity or insulin sensitivity, or high increase rates of insulin clearance, may be an effective strategy to slow down glycemic deterioration in the initial phase of the disease. This reemphasizes the importance of lifestyle interventions aiming at controlling insulin resistance, as preventing deterioration of the other traits currently appears more difficult.

This study also shows that insulin resistance plays a major role in glycemic deterioration in these T2D patients. In particular, we show associations of glycemic deterioration with baseline insulin sensitivity and its longitudinal change that the Belfast Diet Study (1), UKPDS (4,18) and ADOPT (6) could not identify, possibly due to differences in subject selection or to the use of post-MMTT *vs* fasting insulin sensitivity indices. We also demonstrate that the associations between glycemic deterioration and insulin sensitivity are independent from both the baseline value and the progression rate of the *β*-cell function, and that insulin resistance progresses independently from *β*-cell glucose sensitivity. Since in our analysis both HbA_{1c} and insulin sensitivity trajectories were

adjusted for BMI changes and BMI did not increase on average, we can conclude that worsening of insulin resistance in T2D and the associated glycemic deterioration are partly independent from BMI changes. Whether the observed average increases in TG and AST (whose progression rates were inversely correlated with OGIS progression rate) have a role in insulin sensitivity deterioration (19), and whether this is mediated by ectopic fat accumulation (20), deserves further study.

UKPDS 25 and 26 (4,18), the Belfast Diet Study (1) and the ADOPT study (6) identified baseline HOMA-%B as a predictor of glycemic deterioration (insulin requirement within 6 years for UKPDS, time of failure to dietary therapy for the Belfast Diet Study, and monotherapy failure before 4 years for ADOPT). Our study confirms the role of β-cell dysfunction as driver of glycemic deterioration using a dynamic β-cell function assessment based on a glucose challenge, rather than on fasting data only. We show that both baseline β-cell dysfunction (especially β-cell glucose sensitivity) and its deterioration over time are independently associated with HbA_{1c} worsening. Moreover, we demonstrate that patients with limited or absent deterioration in β-cell function have considerably lower odds of rapid glycemic deterioration.

Another novel finding is the strong and independent association between HbA_{1c} progression and insulin clearance during the MMTT, CLIm. To our knowledge, this is the first study examining insulin clearance trajectories after T2D onset. We found that higher baseline CLIm and faster CLIm increase over time independently associate with faster HbA_{1c} progression. This is consistent with the glucose homeostasis mechanisms, as higher CLIm reduces the average insulin levels. Notably, we found a positive correlation between insulin sensitivity and insulin clearance, considering both the baseline values of the two traits, in agreement with previous findings (21), and their progression rates (Figure S2). However, on average, in spite of a decrease in insulin sensitivity, insulin clearance did not decrease. These findings show that, while in pre-diabetic subjects insulin clearance reduction may be a way to mitigate the effects of insulin resistance (22), in T2D patients this compensation appears present but impaired and contributing to glycemic deterioration. The

reasons underlying these results remain elusive. The lack of decrease in insulin clearance may be explained by the decrease of total MMTT insulin secretion and consequent desaturation of insulin utilization (23) only in fast progressors, as in average progressors total insulin secretion slightly increased (Figure 2). Whether hepatic or extrahepatic mechanisms underlie these findings cannot be determined from this study and deserves further investigation.

Our results on TG and HDL effects were partially anticipated by a study of the Genetics of Diabetes Audit and Research (GoDARTS) (24), where the outcome was the risk of progression to insulin treatment. The study identified baseline TG and HDL (besides BMI, sex, and age, year and HbA_{1c} at diagnosis) as independent determinants. A later study on the same data (25), investigating the baseline determinants of HbA_{1c} progression rate over about 9 years, confirmed an independent effect of HDL (together with age, BMI and year at diagnosis) but not of TG. The FIELD study in T2D patients on lifestyle measures only revealed that the HDL effect on initiation of oral hypoglycemic agents survives the adjustment for HOMA-IR (26). Compared to previous studies (24–26) our analysis includes the progression rates of plasma lipid components and baseline MRI assessment of regional fat. We show that baseline HDL and BMI, and the progression rates of TG and HDL are associated with HbA_{1c} progression, even after accounting for the effects of the three main determinants of glucose homeostasis, i.e. insulin sensitivity, β-cell function and insulin clearance. In the subset of participants with MRI data, baseline visceral fat or liver fat was independently correlated with HbA_{1c} progression rate, a further novel observation. These findings suggest that additional lipid-dependent factors contribute to HbA_{1c} deterioration, possible candidates being fat accumulation in the viscera (with excessive supply of fatty acids to the liver (27)), liver fat and consequent hepatic insulin resistance (28), or glucose overproduction (29). The role of visceral/liver fat supports interventions to reduce ectopic fat as a possible way for slowing future glycemic progression.

Previous studies have reported an inverse correlation between baseline age and HbA_{1c} progression (1,4,6,24,25,30). In our analysis, baseline age does not have a clear independent role in the multivariable model, most likely because the age range is relatively narrow relative to other studies, or because the stronger predictors of HbA_{1c} progression are correlated with age. The latter explanation would suggest that the age univariate effect on glycemic deterioration is indirect. We do not find a clear sex effect in glycemic deterioration, in agreement with most previous studies (1,4,6,24,25).

In the multivariable model, baseline HbA_{1c} was independently and inversely correlated with HbA_{1c} progression rate, in contrast with previous findings (1,4,6,24,30). However, baseline HbA_{1c} was not significant in the logistic model. The most likely explanation of this finding is regression to the mean: indeed, a random decrease in baseline HbA_{1c} can produce a higher estimate of HbA_{1c} progression rate, particularly when the follow-up period is not long, as in our study. Tight glycemic control, an inclusion criterion, may have enhanced this effect.

This study does not find a relevant role of other variables often associated with glucose control. In particular, we did not find an effect of smoking status (reported in GPRD (30)), T2D polygenic risk score (in agreement with GoDARTS (24)), baseline values of diet, physical activity, pancreatic fat, GLP-1, and glucagon. Several of these variables were not associated with HbA_{1c} progression rate even in simple correlation analysis (Figure S2). The lack of association for pancreatic fat is particularly relevant, and contributes to the ongoing discussion on the role of pancreas fat in T2D management (31).

In spite of the unique extensive phenotyping of our study and the consistent results, a significant limitation is the relatively short follow-up period (3 years). The accuracy of the estimated HbA_{1c} progression rate over this time frame may be limited, and in a longer time period the factors contributing to progression may differ. In this study, we could not assess the changes over time of relevant variables such as regional fat by MRI, diet and physical activity. MRI measurements were

available only for a subset of subjects. Insulin sensitivity was not derived from the gold standard euglycemic clamp. As the cohort included only patients of white race, our findings are not generalizable to other racial/ethnic groups. Causal relationships could not be inferred from our regression analyses. The study of the mechanisms underlying the deterioration of the factors affecting HbA_{1c} progression, an important aspect to envisage optimal treatment strategies, also requires further investigation.

In summary, based on the extensively phenotyped cohort of white European diabetic patients of the DIRECT study, we identified decreasing insulin sensitivity, deteriorating β-cell function, increasing insulin clearance, high liver or visceral fat, and worsening of the lipid profile as the most important factors independently associated with HbA_{1c} deterioration in the early phase of the disease. We also showed that patients with a relatively stable value over time of at least one of insulin sensitivity, β-cell glucose sensitivity, or insulin clearance have considerably reduced odds of fast HbA_{1c} increase. This study contributes to the understanding of the factors underlying diabetes progression, elucidating the processes that might be targeted for personalized treatments.

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Duality of Interest.

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Eli Lilly, Novo Nordisk and Zoe Global Ltd; he also reports stock options in Zoe Global Ltd. All other co-authors have nothing to disclose.

Author Contributions.

R.B. and A.M. designed the analysis, analyzed the data, and wrote the manuscript. R.B., C.J., A.G.J., M.W., E.R.P. and A.M. interpreted the results. E.R.P. and A.M. supervised the analysis. C.J., A.G.J., A.K., M.W. and E.R.P. reviewed the manuscript. All authors were involved in the DIRECT study at different levels, and were essential for the production, release and management of the data analyzed here. R.B. is the guarantor of this work and, as such, takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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Table 1. Proportion of fast HbA1c progressors with different combinations of stable/deteriorating conditions for GS, OGIS and CLIm progression rates.

Condition*			Average progressors (*N*)	Fast progressors (*N*)	Fast progressors (%) [95% CI]	Odds ratio [95% CI]	p-value†
GS	**OGIS**	**CLIm**					
Deteriorating	Deteriorating	Stable	47	5	9.6 [4.2,20.6]	0.09 [0.02,0.32]	2E-4
Deteriorating	Stable	Deteriorating	56	6	9.7 [4.5,19.5]	0.09 [0.02,0.30]	8E-5
Stable	Deteriorating	Deteriorating	34	3	8.1 [2.8,21.3]	0.07 [0.02,0.32]	4E-4
Deteriorating	Deteriorating	Deteriorating	8	10	55.6 [33.7,75.4]	-	-

* The progression rate thresholds dividing stable and deteriorating traits for OGIS, GS and CLIm are -16.68 ml min^{-1} m^{-2} $year^{-1}$, -4.07 pmol min^{-1} m^{-2} $mmol^{-1}$ l $year^{-1}$ and 0.0184 l min^{-1} m^{-2} $year^{-1}$, respectively.

† Two-sided Chi-square test (α=0.05), with Yates continuity correction, on the proportion of fast progressors in the row compared to the same proportion in the last row.

GS: β-cell glucose sensitivity; OGIS: oral insulin sensitivity; CLIm: mixed meal test insulin clearance.

553 **Figure legends**

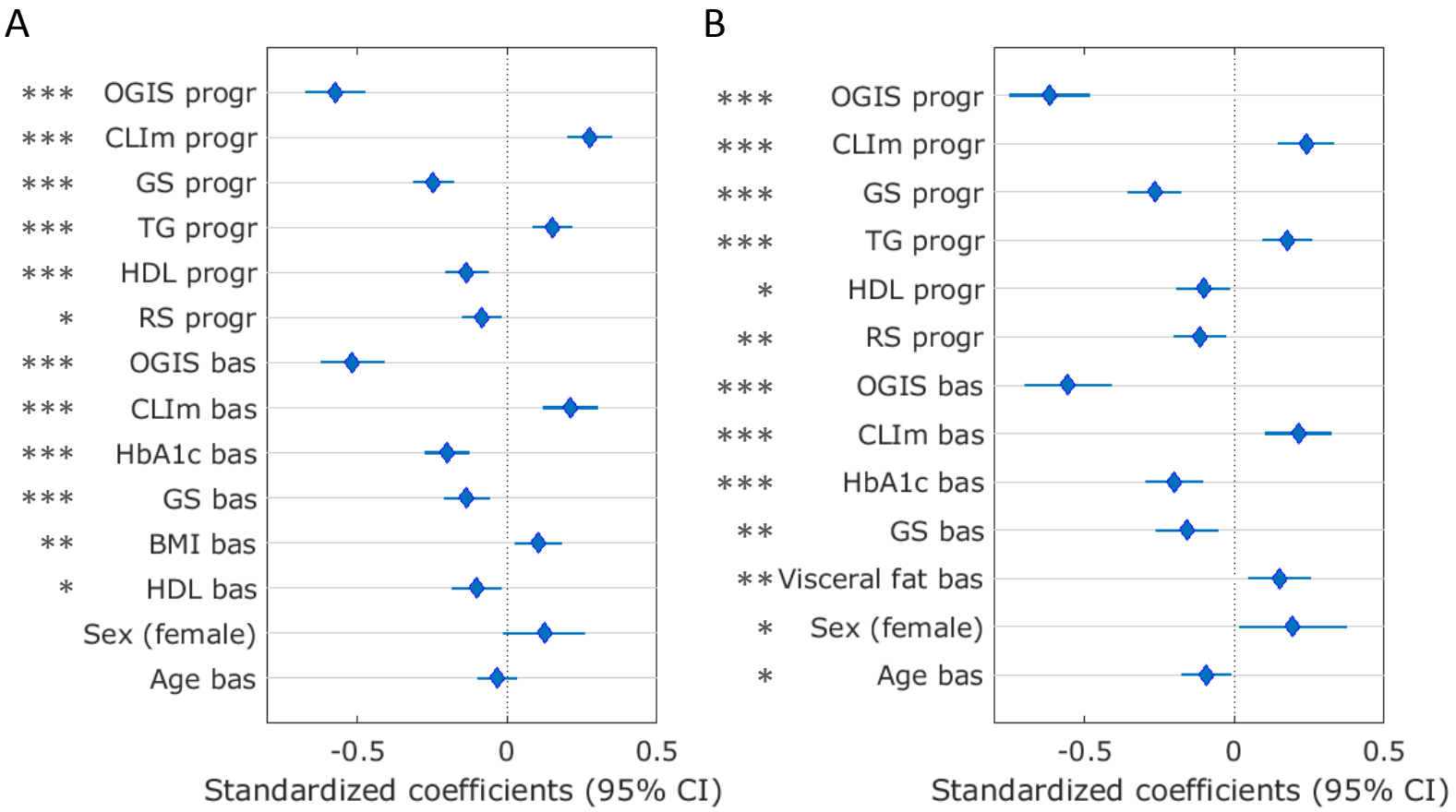
554 Figure 1. Variables independently associated with HbA_{1c} progression rate from multivariable linear
555 analysis. Panel A: all subjects are included in the analysis (625 with all variables), and MRI
556 measurements are not considered; panel B: only subjects with MRI are included in the analysis (374
557 with all variables), and MRI measurements are taken into consideration. For each variable, the
558 figure shows the standardized coefficients ± 95% CI of the effect. Age and HDL were log-
559 transformed. OGIS: oral insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: β-cell
560 glucose sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; RS: β-cell rate
561 sensitivity; progr: progression rate; bas: baseline value; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

562 Figure 2. Temporal trajectories or baseline values (bar graphs) of HbA_{1c} and other key traits in fast
563 (red lines) and average (blue lines) progressors. Data are mean ± standard error. Simple
564 comparisons between fast and average progressors (Wilcoxon rank sum test) are shown for baseline
565 values (asterisks at month 0) and progression rates (asterisks at month 18). These comparisons may
566 differ from the results of the multivariable analyses (Figures 2 and 4). Sex is not included in the
567 figure: males were 42% and 36% in average and fast progressors, respectively (non-significant,
568 Chi-squared test). HbA_{1c} values at 27 months are not displayed as they were collected in a subgroup
569 of individuals. In average progressors, HbA_{1c} increases from 46.4±0.2 mmol/mol to 46.7±0.3
570 mmol/mol; in fast progressors, from 48.9±1.21 mmol/mol to 75.7±2.5 mmol/mol. OGIS: insulin
571 sensitivity; CLIm: mixed meal test insulin clearance; GS: β-cell glucose sensitivity; RS: β-cell rate
572 sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; ISRtot: total mixed meal
573 test insulin secretion; bas: baseline value; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

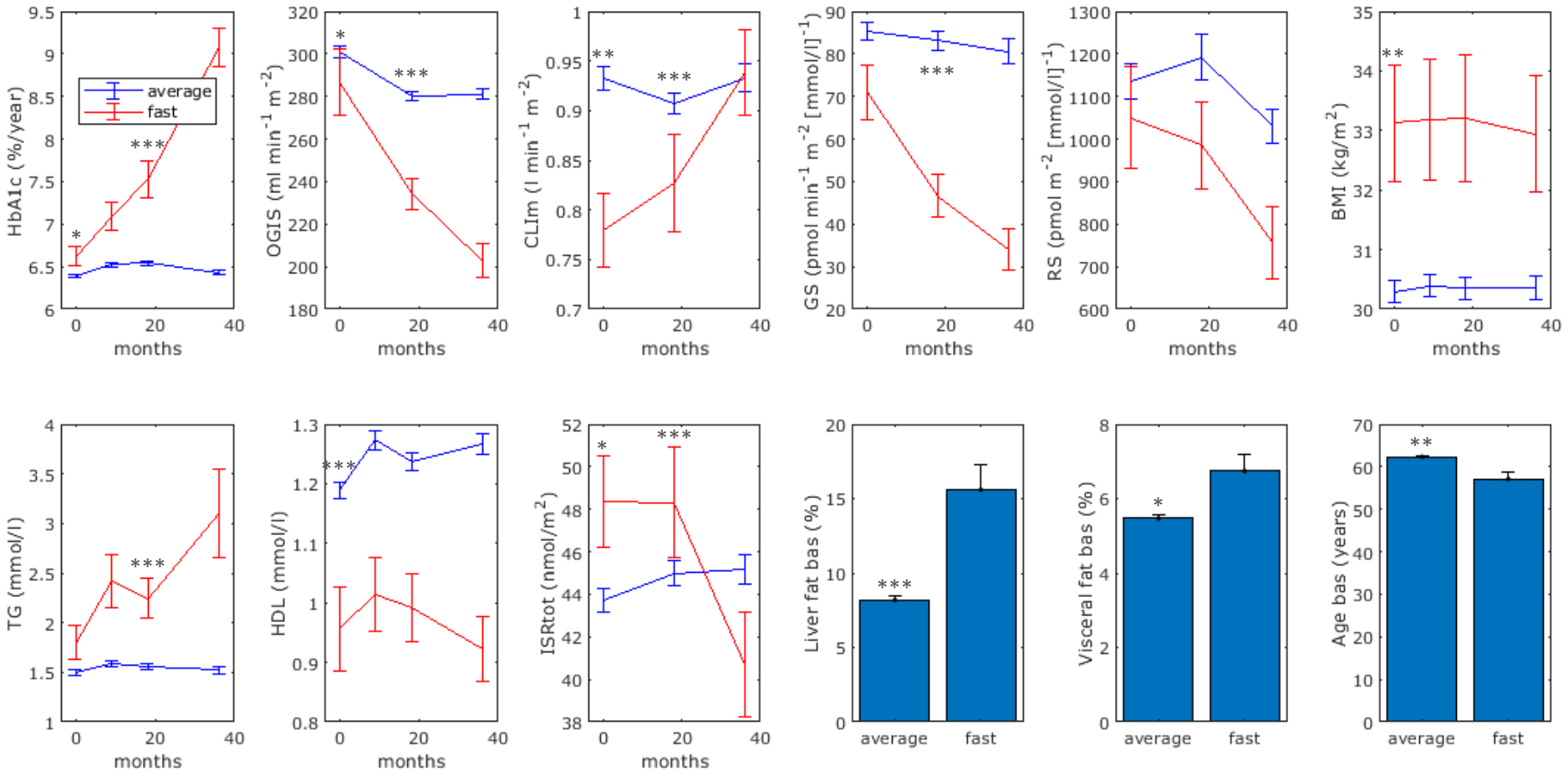
574 Figure 3. Odds ratios ± 95% CI from the multivariable logistic analysis of fast *vs* average HbA_{1c}
575 progressors. The independent variables are those identified by multivariable linear analysis of
576 HbA_{1c} progression, excluding MRI variables (N=625, with 32 fast progressors and 593 average
577 progressors). Age and HDL were log-transformed. Values for sensitivity, specificity and accuracy

were derived via maximization of balanced accuracy. OGIS: insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: β-cell glucose sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; RS: β-cell rate sensitivity; progr: progression rate; bas: baseline value; AUROC: area under the receiver operating characteristics; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

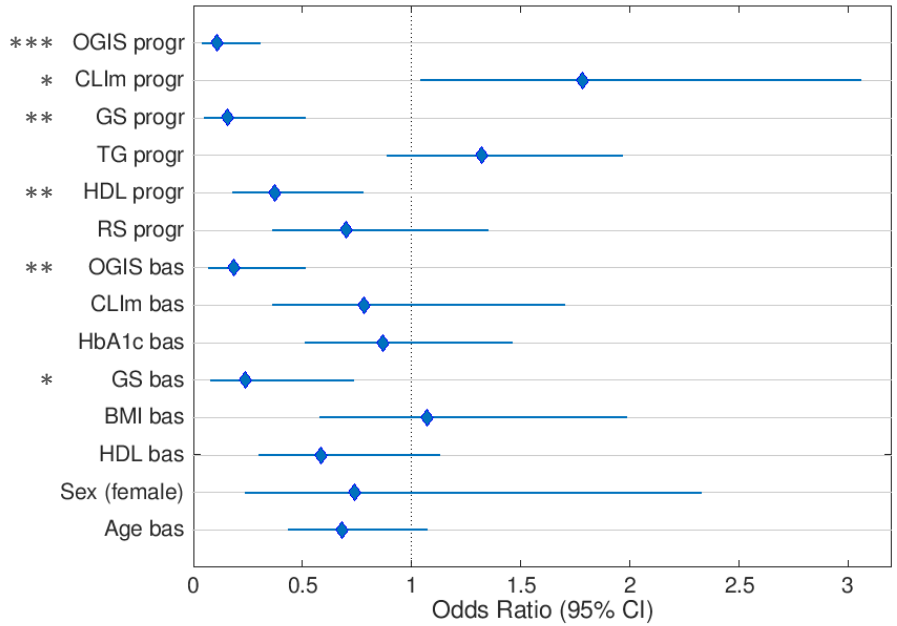
1


A
*** OGIS progr
*** CLIm progr
*** GS progr
*** TG progr
*** HDL progr
* RS progr
*** OGIS bas
*** CLIm bas
*** HbA1c bas
*** GS bas
** BMI bas
* HDL bas
Sex (female)
Age bas
-0.5
0
0.5
Standardized coefficients (95% CI)
B
*** OGIS progr
*** CLIm progr
*** GS progr
*** TG progr
* HDL progr
** RS progr
*** OGIS bas
*** CLIm bas
*** HbA1c bas
** GS bas
** Visceral fat bas
* Sex (female)
* Age bas
-0.5
0
0.5
Standardized coefficients (95% CI)

2


HbA1c (%/year)
average
fast
months
OGIS (ml min-1 m-2)
CLIm (l min-1 m-2)
GS (pmol min-1 m-2 [mmol/l]-1)
RS (pmol m-2 [mmol/l]-1)
BMI (kg/m2)
TG (mmol/l)
HDL (mmol/l)
ISRtot (nmol/m2)
Liver fat bas (%)
Visceral fat bas (%)
Age bas (years)
average
fast

3



AUROC [95% CI]	Sensitivity	Specificity	Accuracy
0.94 [0.87-0.97]	0.84	0.93	0.92

Supplemental Material

SCIENTIFIC MEMBERS OF THE CONSORTIUM

See Table S1.

DATA

Examinations

Examinations were performed in the morning after a 10-hour overnight fast. Participants remained on their usual non-antidiabetic medications; metformin, if used, was stopped for the 24 hours preceding the study visit and restarted immediately after. Anthropometric data, blood pressure, and urine samples were collected. An intravenous cannula was inserted into a forearm vein according to local protocols. Baseline blood samples were immediately collected for analysis of glutamic acid decarboxylase and islet antigen-2 antibodies, glucagon-like peptide-1, glucagon, insulin, C-peptide, HbA_{1c}, and DNA.

Mixed-meal tolerance test (MMTT)

Before the MMTT, fasting samples for glucose, insulin and C-peptide analysis were collected. The MMTT consisted of a 250 ml Fortisip liquid drink (18.4 g carbohydrate per 100 ml) over a period of 2–5 min. Blood samples were collected every 30 min for two hours for subsequent glucose, insulin and C-peptide assays.

Biochemistry assays

Measurements were performed by a central laboratory. Plasma glucose was measured by the enzymatic colorimetric assay GOD-PAP, using Roche MODULAR P analyzers (Hoffmann-La Roche, Basel, Switzerland). Plasma insulin and C-peptide were measured by electrochemiluminescence, using Roche E170 analyzers (Hoffmann-La Roche). HbA_{1c} was measured by ion-exchange high-performance liquid chromatography, using Tosoh G8 analyzers (Tosoh Bioscience, San Francisco, CA, USA).

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured by UV absorbance without pyridoxal phosphate activation. Gamma-glutamyl transferase (GGT) was measured by enzymatic colorimetric assay. Serum creatinine and albumin were measured with the Creatinine Jaffé method and the bromocresol green method, respectively. Cholesterol was measured by enzymatic colorimetric methods, HDL-cholesterol was measured directly using PEG-modified enzymes and dextran sulphate, triacylglycerol was measured by quantitative determination with glycerol blanking. AST, ALT, GGT, serum creatinine and albumin, cholesterol, HDL-cholesterol and triacylglycerol were measured using a Roche MODULAR P analyzer (Roche Diagnostics, Indianapolis, IN, USA). LDL-cholesterol was calculated from the Friedewald formula.

Intact proinsulin was measured using the TECO Medical Intact Proinsulin ELISA kit in use on the Dynex DS2 analyzer. Glucagon, glutamic acid decarboxylase (GAD) and islet antigen-2 antibodies (IA-2) were measured using a DS2 Elisa robot, Dynex technologies.

Plasma samples for glucagon-like peptide-1 (GLP-1) measurement were collected in P800 tubes (Becton Dickinson, Wokingham, UK) to prevent intrinsic proteolysis. Intact GLP-1 was measured using MSD GLP-1 active kit (product code K150JWC; Meso Scale Diagnostics, Rockville, MD, USA). Total GLP-1 was assayed using MSD GLP-1 total kit (product code K150JVC; Meso Scale Diagnostics).

Each biochemical assay was performed using validated standard methods. Reference samples were included in all procedures to control for inter-assay variation, and the laboratory regularly participated in international external quality assessment schemes.

Body composition

Body mass index (BMI) was calculated as weight divided by height squared, and waist circumference was measured at the level of the umbilicus at mid-respiration. The hepatic steatosis index (HSI) was calculated as described previously (1).

Abdominal MRI

The volume of adipose tissue was measured using MRI, as described elsewhere (2). Total abdominal adipose tissue was separated into intra-abdominal adipose tissue, also referred to as “visceral” fat, and abdominal subcutaneous adipose tissue. Liver and pancreas fat and iron were derived simultaneously using a multiecho MRI technique (2–4).

Dietary data

Self-reported dietary intake was assessed by 24-hour multi-pass method, using food habit and 24-hour recall questionnaires. Nutritional analysis was undertaken using Dietplan-7 software (Forestfield Software Ltd, Horsham,

UK). All diet coders were trained by a lead research dietician/nutritionist using a study specific operational manual protocol. Detailed description of the coding and diet analysis protocol are reported elsewhere (5).
Dietary patterns were assessed in concordance with the WHO dietary guidelines using the validated "Healthy Diet Indicator" (HDI) (6); a higher HDI score indicates a more favorable diet. The score was calculated from the dietary intakes of all food and drink consumed except alcohol, which was analyzed separately.

Physical activity intensity and sedentary behaviour
Participants were fitted with a wrist-worn triaxial accelerometer (ActiGraph GT3X+; Actigraph LLC, Pensacola, FL, USA) for measurement of physical activity, sedentary behavior and sleep over 10 days. The monitor was fitted to the participant's non-dominant wrist using an adjustable strap. The participant was requested to wear the monitor continuously for 10 days to allow habitual uninterrupted measures of both sleep and physical activity. The monitor was set to record at 30 Hz with the manufacturer's sleep mode disabled. High-pass-filtered vector magnitude (hpfVM) was derived as described elsewhere (7). In this analysis, we used the 10-day mean hpfVM and the percentage of hpfVM values $\leq$ 48 m*g* as measures of physical activity intensity and sedentary behavior.

Type 2 diabetes (T2D) polygenic risk score
A T2D polygenic risk score was computed from the 403 single-nucleotide polymorphisms (SNPs) and the respective effect sizes reported for T2D in Mahajan et al. (8). The individual score values were obtained by summing up the number of risk alleles at each locus multiplied by its effect size.

Additional questionnaires
Questionnaire data were collected on alcohol consumption, smoke habits, family history of diabetes and medication history.

The whole set of traits considered in this study is reported in Table S2.

METHODS

Area under the curves and mean values
Areas under the curve (AUC) of several MMTT variables were computed according to the trapezoidal rule and mean values as AUC/time interval.

Mathematical modelling of β-cell function
From MMTT glucose and C-peptide, the following β-cell function parameters were calculated by mathematical modelling (9): glucose sensitivity (GS), i.e., the slope of the relationship between glucose concentration and insulin secretion rate; rate sensitivity (RS), marker of early insulin release; insulin secretion rate at 8 mmol/l glucose (ISRstd); potentiation factor ratio (PR), the ratio between the potentiation factor at 2- and 0-hours, ; total insulin secretion (ISRtot), i.e., the AUC of insulin secretion during the whole MMTT. Insulin secretion rate was calculated from C-peptide using Van Cauter's C-peptide model (10).

Insulin clearance
Fasting insulin clearance (CLIb) was calculated as the ratio between fasting insulin secretion and fasting insulin concentration. The MMTT insulin clearance (CLIm) was calculated as the ratio of the AUCs of insulin secretion and insulin concentration during the MMTT.

Mathematical modelling of HbA_{1c} progression rate
The HbA1c trajectories were described with a conditional linear mixed-effect model (11). The conditional approach employs a linear transformation of the data to derive a longitudinal and a cross-sectional component, which are orthogonal. The transformation makes modelling of the longitudinal component independent of the cross-sectional effects: the former is relevant for quantification of HbA_{1c} progression rate, while the latter are potential confounders that need not to be considered in the conditional approach. In particular, the approach eliminates possible spurious correlations between the longitudinal parameters and baseline HbA_{1c}, which may arise if baseline HbA_{1c} is not accurately modelled.
The longitudinal HbA_{1c} component was described as the sum of the following terms:

- a proportional effect of time, described by the parameter r_i, where *i* represents a specific individual, represented as a random variable with a normal distribution;
- a proportional effect of BMI;
- a linear effect of the metformin dose, expressed as percentage of a maximal dose of 3 grams;

- a linear effect of the cumulative dose for the other antidiabetic drugs (insulin excluded), expressed as sum of the percentages of the maximum dose of each drug;
- a constant effect of insulin treatment;
- a proportional effect of delay in HbA_{1c} assay, i.e. of the difference between the time of measurement and the time of sample collection;
- a residual error ε_{ik}, where k refers to the time point, represented as a random variable from a normal distribution with zero mean.

The insulin and BMI effects were constrained to be negative and positive, respectively. The linear effects of the treatment *dose* were modelled as 0 for *dose*=0, and as $a+b \cdot dose$ for *dose*>0, where a and b were different for metformin and the other antidiabetic drugs and were constrained to be negative. Maximum doses for antidiabetic drugs different from metformin and insulin were fixed to the values in Table S3. A medication was considered effective at a given time if it was taken at least 30 days before.
The r_i parameter represents the HbA_{1c} underlying progression rate, adjusted for changes in BMI and antidiabetic treatments.
The model parameters were estimated using Monolix 2016 R1(12), which implements the SAEM algorithm for estimation of mixed-effect models. In a first step, the software identifies mean and standard deviation of the population distribution of the model parameters with inter-individual variability (in our case just r). In the second step, the software computes the individual estimates of the parameters (in our case r_i) by simultaneously fitting the data and using the previously estimated distributions as priors (*maximum a posteriori* estimation).
The parameter estimates of the HbA_{1c} progression model are reported in Table S4. The BMI and treatment effects were concordant with what shown in the literature(13), considering the low baseline HbA_{1c} values in this study (6.41±0.53 %, 46.5±5.8 mmol/mol, mean ± standard deviation).

Progression rates for other traits
The progression rates for all other traits were derived in the same way as for HbA_{1c}, but without including the effect of treatments and assay delay. The BMI effect was included only in the models for OGIS and QUICKI. The BMI effects on OGIS and QUICKI progression rates were -8.68±11% (estimate±relative standard error) ml min^{-1} kg^{-1} and -0.00157±9% m^2 kg^{-1}, respectively.

On the multivariable analyses
Baseline values of the β-cell function parameters of some subjects were discarded due to high uncertainty in their estimates.

RESULTS

Progression rates of HbA_{1c} and other traits
HbA_{1c} was measured at two visits in 6% of participants, at three visits in 15% of participants, at four visits in 75% of participants, and at five visits in 4% of participants.
In 50% of the subjects, T2D was managed via lifestyle only along the whole study.
The estimates of the progression rates for HbA_{1c}, adjusted for changes in BMI and in diabetes medications, and for the other traits are reported in Figure S1 (histogram for HbA_{1c} progression rates only) and Table S5.

Variables associated with HbA_{1c} progression rate
The pairwise associations between HbA_{1c} progression rate and baseline values and progression rates of the investigated traits are shown in Figure S2.
The standardized coefficients and the p values of the independent variables included in the multivariable linear analysis of HbA_{1c} progression rate are shown in Table S6. The table presents different regression models, all adjusted for sex, baseline age and center, and considering different subsets of subjects, based on the availability of different subsets of variables. The models described include those with a unique independent variable (models named "-1"), a model with the adjustment variables only (model "0"), and models including or excluding the effects of baseline liver fat or visceral fat, and the effects of baseline BMI and fasting HDL-cholesterol, found to have non-significant effects once visceral or liver fat is included in the analysis. The models presented in the main text are numbered "1" and "9".
In the multivariable linear analysis, the indices of insulin sensitivity OGIS and QUICKI, as well as HOMA-IR (14), Stumvoll (15) and Matsuda (16) indices (data not shown), were interchangeable in terms of overall analysis results, with OGIS producing the best performance (adjusted R^2 0.38 *vs* 0.33, 0.37, 0.28 and 0.29, respectively; N = 625).

Variables associated with fast *vs* average HbA_{1c} progression
The logistic analysis reported in the main text defines fast *vs* average progressors based on a threshold on HbA_{1c} progression rate that clearly separate the two groups (0.255 %/year, 2.79 mmol mol^{-1} $year^{-1}$, Figure S1). We found that

this threshold corresponds to (q_{50} - q_1) + q_{50}, where q_1 and q_{50} are the 1st and 50th quantiles of the distribution of individual HbA_{1c} progression rates. The use of lower thresholds allows the identification of larger sets of fast progressors. In particular, using the 2nd, 5th or 10th quantile instead of the 1st quantile in the formula, thresholds of 0.200, 0.143 or 0.121 %/year (2.19, 1.56 or 1.32 mmol mol^{-1} $year^{-1}$), respectively, are obtained, with a corresponding number of fast progressors of *N*=61, *N*=110 or *N*=131 subjects, respectively, instead of *N*=33 (Figure S1).
With the lower thresholds, discrimination capacity, sensitivity, specificity and accuracy of the logistic model described in the main text remain very similar (Figure S3). The effects of the independent variables of the logistic model are also essentially unaffected (Figure S3). In all cases, it appears that stronger deterioration and a lower baseline value of OGIS and GS, and CLIm increase are independently associated with fast progression. Minor differences are the following: the effect of HDL reduction is significant with all thresholds apart from 0.200 %/year; the effect of baseline HDL is significant only using thresholds 0.143 and 0.121 %/year; the effect of baseline CLIm is significant only with the lowest threshold (0.121 %/year); the effect of baseline HbA_{1c} is significant with all lower thresholds but not with the original one.
The percentage of patients without diabetes medications along the whole study was higher in average than in fast progressors (51% *vs* 30%, *p*=0.021 from two-sided Chi-square test with α=0.05). At baseline, the percentages of fast progressors and of average progressors treated with metformin were not different: 39.4% [24.7-56.3%, 95% CI] *vs* 33.9% [30.5-37.5%], respectively (*p* = 0.64). At the last visit, the percentage of fast progressors treated with any diabetes medication, 66.7% [49.6-80.2%], was somewhat higher than the percentage of average progressors treated with any diabetes medication, 47.5% [43.8-51.2%] (*p* = 0.048). This difference was driven by a larger use of diabetes medications other than metformin or insulin in fast progressors (30.3% [17.4-47.3%] *vs* 5.0% [3.6-6.9%], *p* = 3E-8). Again at the last visit, the number of patients treated with insulin (seven average progressors) was too low to derive any trustworthy comparison between percentages of fast and average progressors treated with insulin (0.0% [0.0-10.4%] and 1.0% [0.5-2.1%], respectively, *p* = 0.74).

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Table S2. Subjects' baseline traits.

Trait	Abbreviation	Baseline value*	*N*
Age (years)	age	62±8	732
Sex (males)	-	58	732
Body mass index (kg/m^2)	BMI	30.4±4.9	732
Waist circumference (cm)	waist	103±13	727
Systolic blood pressure (mm Hg)	BPsys	131±16	621
Diastolic blood pressure (mm Hg)	BPdia	75±10	621
Type 2 diabetes family history	-	39	682
On metformin†	-	34	732
Metformin dosage for subjects on metformin (g)†	-	1.0±0.5	732
HbA_{1c} (%, mmol/mol)	HbA_{1c}	6.41±0.53, 46.5±5.8	728
Fasting glucose (mmol/l)†	gb	7.1±1.4	731
Fasting insulin (pmol/l)†	ib	106±69	730
Mean MMTT glucose (mmol/l)†	gm	9.3±2.1	730
Mean MMTT insulin (pmol/l)†	im	459±279	730
Fasting insulin secretion (pmol min^{-1} m^{-2})†	ISRb	136±48	730
Total MMTT insulin secretion (nmol/m^2)†	ISRtot	44±15	730
Fasting triacylglycerol (mmol/l)	TG	1.51±0.78	732
Fasting total cholesterol (mmol/l)	CHO	4.22±1.15	732
Fasting LDL-cholesterol (mmol/l)	LDL	2.34±0.95	727
Fasting HDL-cholesterol (mmol/l)	HDL	1.18±0.39	732
Aspartate aminotransferase (U/l)	AST	25.6±11.1	732
Alanine aminotransferase (U/l)	ALT	26.2±13.8	732
AST/ALT ratio (unitless)	AST/ALT	1.09±0.48	732
Gamma-glutamyl transferase (U/l)	GGT	51±71	732
Serum creatinine (µmol/l)	SCr	74.7±17.9	732
Serum albumin (g/l)	ALB	39.7±2.6	165
Fasting intact glucagon-like peptide-1 (pg/ml)	iGLP1	0.64±0.91	725
Fasting total glucagon-like peptide-1 (pg/ml)	tGLP1	9.5±9.3	724
1-h total glucagon-like peptide-1 (pg/ml)	tGLP1.60	19±16	722
Fasting glucagon (pg/ml)	GLG	111±52	704
1-h glucagon (pg/ml)	GLG.60	107±39	717
2-h glucagon (pg/ml)	GLG.120	103±25	184
1-h GLP-1 increment (pg/ml)	GLP1inc.60	9.8±12.7	718
1-h glucagon increment (pg/ml)	GLGinc.60	-3±52	693
2-h glucagon increment (pg/ml)	GLGinc.120	-6±33	183
1-h intact proinsulin (pmol/l)	proins.60	22±14	359
1-h intact proinsulin to insulin ratio (unitless)	proins/ins.60	0.05±0.04	358
Insulin sensitivity (ml min^{-1} m^{-2})	OGIS	300±74	728
Fasting insulin sensitivity (unitless)	QUICKI	0.136±0.014	730
β-cell glucose sensitivity (pmol min^{-1} m^{-2} mmol^{-1} l)	GS	85±56	714
β-cell rate sensitivity (pmol m^{-2} mmol^{-1} l)	RS	1138±1102	714
Insulin secretion rate at 8 mmol/l glucose (pmol min^{-1} m^{-2})	ISRstd	228±135	714
Potentiation factor ratio (unitless)	PR	1.4±0.6	713
Fasting insulin clearance (l min^{-1} m^{-2})	CLIb	1.60±1.02	730
MMTT insulin clearance (l min^{-1} m^{-2})	CLIm	0.93±0.30	730
Hepatic steatosis index (unitless)	HSI	41.5±5.9	730
Fatty liver index (unitless)	FLI	67±27	725
Type 2 diabetes polygenic risk score (unitless)	PRS	25.2±0.7	732
Liver fat (%)	liver fat	9±7	480

Trait	Abbreviation	Baseline value*	*N*
Liver iron content (mg/g tissue)	liver iron	1.6±0.5	486
Pancreas fat (%)	pancreas fat	12±8	488
Pancreas iron content (mg/g tissue)	pancreas iron	1.4±0.5	509
Intra-abdominal adipose tissue (l)	visceral fat	5.5±2.2	429
Abdominal subcutaneous adipose tissue (l)	subcutaneous fat	8.0±3.7	429
Physical activity intensity (m*g*)	PA	35±10	674
Sedentary behavior (% of time)	SED	83±4	674
Smoking habits (%, current, ex, never)	-	13, 50, 37	732
Average alcohol consumption (%, regularly, occasionally, never)	-	58, 25, 17	732
24-h energy intake (kcal)	-	1828±625	644
24-h protein intake (g)	-	89±35	644
24-h fat intake (g)	-	73±34	644
24-h saturated fat intake (g)	-	26±14	644
24-h added sugars intake (g)	-	65±40	644
24-h carbohydrate intake (g)	-	221±91	644
24-h energy intake-adjusted non-starch polysaccharides (g/kcal)	-	8.7±3.3	644
24-h energy intake-adjusted fruit & vegetables (g/kcal)	-	227±145	644
24-h energy intake-adjusted wholegrains (g/kcal)	-	26±22	644
24-h energy intake-adjusted fish (g/kcal)	-	20±39	644
24-h energy intake-adjusted red meat (g/kcal)	-	46±49	644
24-h percentage of total energy intake from protein (%)	-	20±6	644
24-h percentage of total energy intake from fat (%)	-	36±9	644
24-h percentage of total energy intake from saturated fat (%)	-	13±5	644
24-h percentage of total energy intake from added sugars (%)	-	19±8	644
24-h percentage of total energy intake from carbohydrate (%)	-	49±11	644
Healthy diet indicator	HDI	4.7±2.6	644
Healthy diet indicator quartiles (% in quartiles 1, 2, 3 and 4)	-	23, 25, 26, 26	644

* Data are mean ± standard deviation of the inter-individual distribution, or percentage.

† Trait not included in the stepwise multivariable analyses.

MMTT: mixed meal test.

Table S3. Maximum doses for antidiabetic drugs different from insulin.

Drug	Max Dose (mg)	Weekly (W) or Daily (D)
Acarbose	600	D
Metformin	3000	D
Dapagliflozin	10	D
Empagliflozin	25	D
Alogliptin	25	D
Sitagliptin	100	D
Dulaglutide	1.5	W
Liraglutide	1.8	D
Gliclazide	320	D
Glimepiride	4	D
Glipizide	20	D
Tolbutamide	2000	D

Table S4. Parameter estimates of the HbA_{1c} progression model.

Parameter	Estimate	RSE (%)
r (%/year, mmol mol^{-1} $year^{-1}$)	0.0627, 0.685*	17
BMI effect (% kg^{-1} m^{-2}, mmol mol^{-1} kg^{-1} m^{-2})	0.131, 1.43	8
Metformin effect: *a* (%, mmol/mol)	-0.0942, -1.03	74
Metformin effect: *b* (%, mmol/mol)	-0.00145, -0.0159	101
Metformin effect with 100% dose (%, mmol/mol)	-0.240, -2.62	-
Other antidiabetic treatment effect: *a* (%, mmol/mol)	-0.0970, -1.06	153
Other antidiabetic treatment effect: *b* (%, mmol/mol)	-0.00161, -0.0176	138
Other antidiabetic treatment effect with 100% dose (%, mmol/mol)	-0.258, -2.82	-
Insulin effect (%, mmol/mol)	-0.0970, -1.06	205
Assay delay effect (%/day, mmol mol^{-1} day^{-1})	-0.00047, -0.00516	19

RSE: relative standard error of the estimate.

* Mean value of the population distribution.

Table S5. Estimates of the progression rates of the investigated traits.

Trait	Abbreviation	Progression rate*	95% CI	Relative progression rate†	*N*
Body mass index (kg m^{-2} $year^{-1}$)	BMI	-0.0089±0.52	-0.058,0.040	-0.03	732
Waist circumference (cm $year^{-1}$)	waist	0.54±1.3	0.37,0.71	0.52	719
HbA_{1c} (%/year, mmol mol^{-1} $year^{-1}$)	HbA_{1c}	0.063±0.18, 0.69±2.0	0.041,0.085, 0.45,0.93	0.98, 1.47	732
Total MMTT insulin secretion (nmol m^{-2} $year^{-1}$)‡	ISRtot	0.44±2.4	0.13,0.75	1.00	653
Fasting triacylglycerol (mmol l^{-1} $year^{-1}$)	TG	0.038±0.14	0.016,0.060	2.50	719
Fasting total cholesterol (mmol l^{-1} $year^{-1}$)	CHO	-0.012±0.22	-0.039,0.015	-0.28	719
Fasting LDL-cholesterol (mmol l^{-1} $year^{-1}$)	LDL	-0.046±0.18	-0.070,-0.023	-1.94	713
Fasting HDL-cholesterol (mmol l^{-1} $year^{-1}$)	HDL	0.016±0.040	0.009,0.023	1.36	719
Aspartate aminotransferase (U l^{-1} $year^{-1}$)	AST	1.2±3.6	0.77,1.63	4.77	719
Alanine aminotransferase (U l^{-1} $year^{-1}$)	ALT	0.53±10	-0.39,1.45	2.01	719
AST/ALT ratio ($year^{-1}$)	AST/ALT	0.039±0.04	0.024,0.054	3.61	719
Serum creatinine (µmol l^{-1} $year^{-1}$)	SCr	-0.21±1.2	-0.58,0.16	-0.29	719
Insulin sensitivity (ml min^{-1} m^{-2} $year^{-1}$)	OGIS	-8.5±19	-10.7,-6.3	-2.82	649
Fasting insulin sensitivity ($year^{-1}$)	QUICKI	-0.0013±0.0025	-0.0016,-0.0010	-0.95	653
***β*-cell glucose sensitivity (pmol min^{-1} m^{-2} $mmol^{-1}$ l $year^{-1}$)**	GS	-1.9±5.0	-3.4,-0.4	-2.19	653
***β*-cell rate sensitivity (pmol m^{-2} $mmol^{-1}$ l $year^{-1}$)**	RS	-22±98	-57,13	-1.91	653
Insulin secretion rate at 8 mmol/l glucose (pmol min^{-1} m^{-2} $year^{-1}$)	ISRstd	-5.2±19	-8.5,-1.9	-2.29	653
Potentiation factor ratio ($year^{-1}$)	PR	-0.0035±0.11	-0.023,0.016	-0.25	652
Fasting insulin clearance (l min^{-1} m^{-2} $year^{-1}$)	CLIb	-0.039±0.34	-0.070,-0.008	-2.46	653
MMTT insulin clearance (l min^{-1} m^{-2} $year^{-1}$)	CLIm	-0.00069±0.046	-0.0072,0.0058	-0.07	653
Hepatic steatosis index ($year^{-1}$)	HSI	-0.31±0.68	-0.40,-0.22	-0.74	717

* Data are mean ± standard deviation of the inter-individual distribution, and are expressed as units/year (e.g. %/year or mmol mol^{-1} $year^{-1}$ for HbA_{1c}).

† Ratio between mean progression rate and mean baseline value (from Table S2), as percentage per year.

‡ Progression rate not included in the stepwise multivariable analyses.

CI: confidence interval on the estimate of the mean; MMTT: mixed meal test.

Table S6. Standardized coefficients (with *p* values as superscripts) and adjusted R^2 from multivariable linear analysis of HbA_{1c} progression rate.

Model	Sex	Age bas	OGIS progr	CLIm progr	GS progr	TG progr	HDL progr	RS progr	OGIS bas	CLIm bas	HbA_{1c} bas	GS bas	BMI bas	HDL bas	Visceral fat bas	Liver fat bas	Adjusted R^2	*N*
-1	-	-	-0.24***	0.16***	-0.23***	0.25***	-0.11**	$-0.07^{0.07}$	-0.11**	-0.11**	$0.02^{0.58}$	$-0.06^{0.13}$	0.15***	-0.18***	0.27***	0.19***	-	625*
0	$-0.04^{0.61}$	-0.15***	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.04	625
1	$0.12^{0.08}$	$-0.03^{0.31}$	-0.57***	0.28***	-0.25***	0.15***	-0.14***	-0.09*	-0.52***	0.21***	-0.20***	-0.14***	0.10**	-0.10*	-	-	0.38	625
2	0.21*	-0.08*	-0.61***	-0.08*	-0.27***	0.30***	-0.11*	0.13**	-0.53***	0.22***	-0.22***	-0.15**	$0.09^{0.07}$	$-0.05^{0.37}$	-	-	0.40	407 (liver fat bas available)
3	$0.15^{0.10}$	$-0.06^{0.16}$	-0.60***	-0.12**	-0.28***	0.25***	-0.14**	0.17***	-0.57***	0.22***	-0.20***	-0.17**	$0.06^{0.24}$	$-0.11^{0.05}$	-	-	0.40	373 (visceral fat bas available)
4	0.18*	$-0.08^{0.06}$	-0.59***	-0.08*	-0.28***	0.30***	-0.11*	0.13**	-0.49***	0.24***	-0.24***	-0.16**	$0.08^{0.10}$	$-0.03^{0.51}$	-	0.10*	0.40	407
5	0.25*	$-0.08^{0.06}$	-0.58***	-0.12**	-0.27***	0.24***	-0.13**	0.17***	-0.55***	0.24***	-0.21***	-0.16**	$0.01^{0.87}$	$-0.11^{0.06}$	0.14*	-	0.41	373
6	$0.14^{0.14}$	$-0.08^{0.7}$	-0.63***	0.25***	-0.26***	0.17***	-0.10*	-0.10*	-0.54***	0.21***	-0.21***	-0.16**	-	-	-	0.12*	0.40	320 (both visceral fat bas and liver fat bas available)
7	0.26**	-0.11*	-0.63***	0.25***	-0.25***	0.16***	$-0.08^{0.10}$	-0.11*	-0.56***	0.23***	-0.20***	-0.14*	-	-	0.16**	-	0.41	320 (both visceral fat bas and liver fat bas available)
8	0.17*	-0.09*	-0.61***	0.30***	-0.27***	0.13**	-0.10*	$-0.08^{0.06}$	-0.50***	0.19***	-0.23***	-0.16**	-	-	-	0.11*	0.40	408
9	0.19*	-0.09*	-0.62***	0.24***	-0.16**	0.18***	-0.10*	-0.12**	-0.56***	0.21***	-0.20***	-0.16**	-	-	0.15**	-	0.40	374

Model (-1): HbA_{1c} progression rate = sex + age bas + center + variable (each column represents a specific model, and the various models are given in a unique row for sake of clarity).
Model (0): HbA_{1c} progression rate = sex + age bas + center.
Model (1): HbA_{1c} progression rate = sex + age bas + center + OGIS progr + CLIm progr + GS progr + TG progr + HDL progr + RS progr + OGIS bas + CLIm bas + HbA_{1c} bas + GS bas + BMI bas + HDL bas. This is the model in Figure 1, panel A.
Model (2): Model (1), with different *N* (see last column).
Model (3): Model (1), with different *N* (see last column).
Model (4): Model (1) + liver fat bas.
Model (5): Model (1) + visceral fat bas.
Model (6): HbA_{1c} progression rate = Sex + Age bas + center + OGIS progr + CLIm progr + GS progr + TG progr + HDL progr + RS progr + OGIS bas + CLIm bas + HbA_{1c} bas + GS bas + liver fat bas.
Model (7): HbA_{1c} progression rate = Sex + Age bas + center + OGIS progr + CLIm progr + GS progr + TG progr + HDL progr + RS progr + OGIS bas + CLIm bas + HbA_{1c} bas + GS bas + visceral fat bas.
Model (8): Model (6), with different *N* (see last column).
Model (9): Model (7), with different *N* (see last column). This is the model in Figure 1, panel B.
* *N* = 320 for columns Visceral fat bas and Liver fat bas.
OGIS: insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: β-cell glucose sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; RS: β-cell rate sensitivity; BMI: body mass index; progr: progression rate; bas: baseline value; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

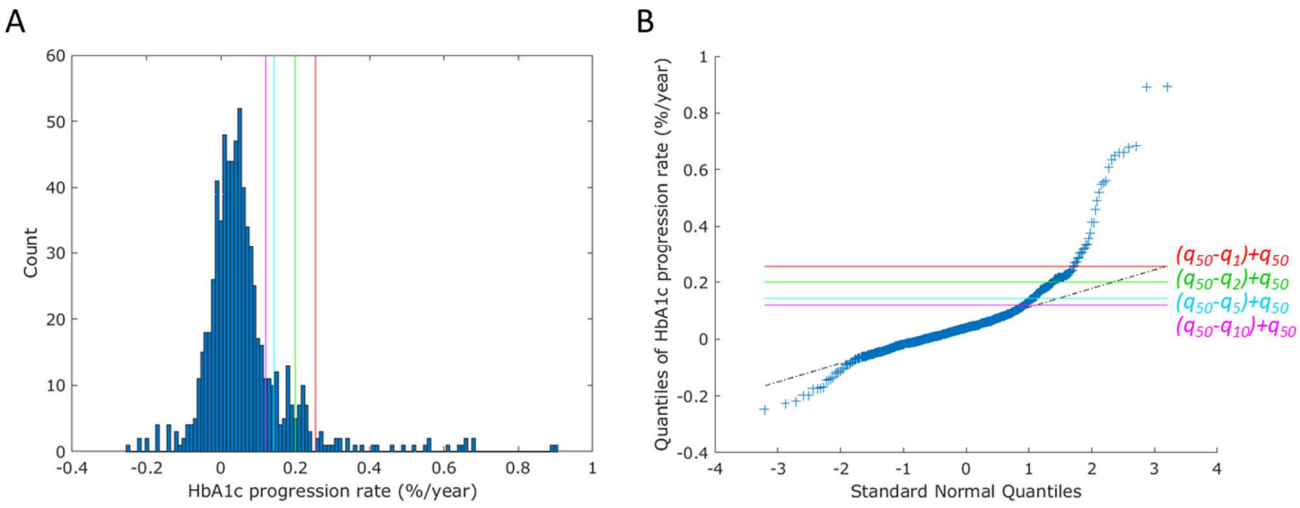


Figure S1. Distribution of the estimated individual progression rates of HbA_{1c} (*N*=732), adjusted for changes in BMI and anti-diabetic medications. Panel A: histogram. Panel B: quantile-quantile plot. In both panels, four straight solid lines show four different thresholds used to split subjects into average and fast progressors. The thresholds were computed as $(q_{50} - q_n) + q_{50}$, where q_n and q_{50} are the n^{th} and 50^{th} quantiles of the distribution: the threshold used in the main text (n=1) is shown in red, three less conservative thresholds (n=2, 5 and 10) are shown in green, light blue and purple, respectively.

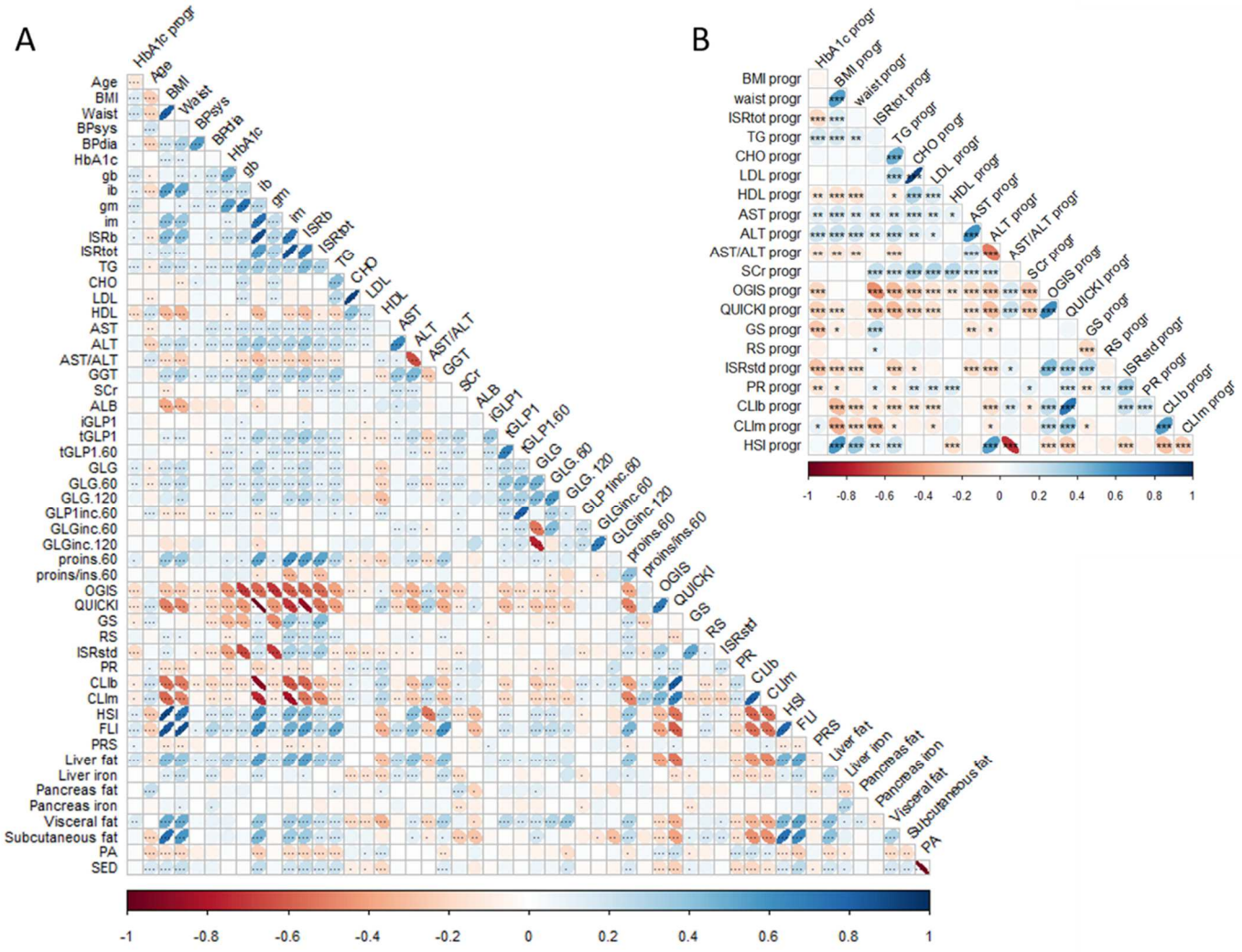
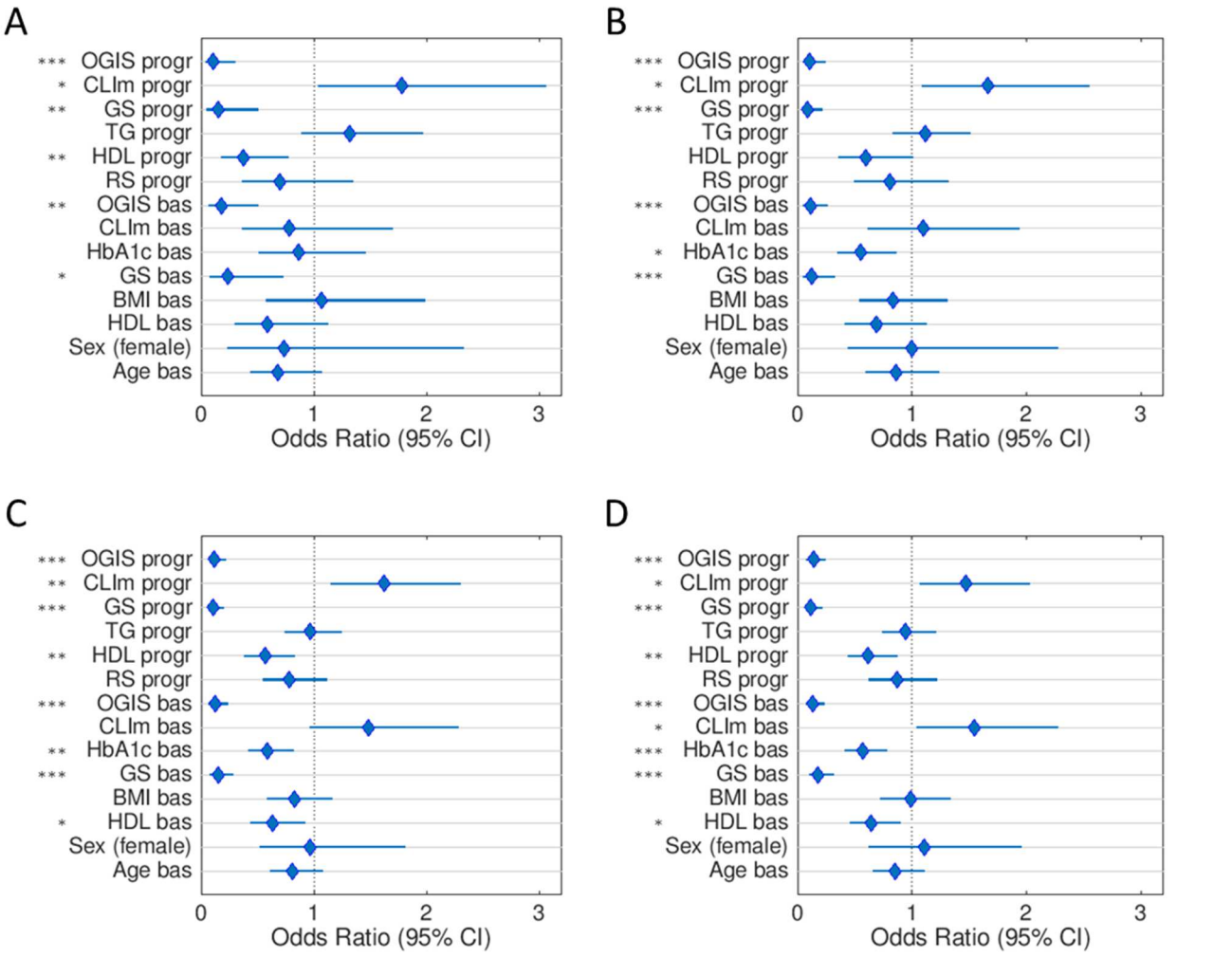


Figure S2. Pairwise correlation matrixes of the variables considered in this study (diet variables excluded as none was associated with HbA1c progression rate). Panel A: pairwise correlations among baseline values of the traits and HbA_{1c} progression rates. Panel B: pairwise correlations among all the estimated progression rates. Correlations with HbA_{1c} progression rates are displayed in the first columns of both panels. Fill color represents Spearman correlation coefficient, where positivity is denoted by red fill, negativity by blue fill, and magnitude by color intensity (see color bars) and by elliptic shape. BMI: body mass index; BPsys: systolic blood pressure; BPdia: diastolic blood pressure; gb: fasting glucose; ib: fasting insulin; gm: mean mixed meal test (MMTT) glucose; im: mean MMTT insulin; ISRb: fasting insulin secretion (ISR); ISRtot: total MMTT insulin secretion; TG: fasting triacylglycerol; CHO: fasting total cholesterol; LDL: fasting LDL-cholesterol; HDL: fasting HDL-cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AST/ALT: AST/ALT ratio; GGT: gamma-glutamyl transferase; SCr: serum creatinine; ALB: serum albumin; iGLP1: fasting intact glucagon-like peptide-1 (GLP-1); tGLP1: fasting total GLP-1; tGLP1.60: 1-h total GLP-1; GLG: fasting glucagon; GLG.60: 1-h glucagon; GLG.120: 2-h glucagon; GLP1inc.60: 1-h GLP-1 increment; GLGinc.60: 1-h glucagon increment; GLGinc.120: 2-h glucagon increment; proins.60: 1-h intact proinsulin; proins/ins.60: 1-h intact proinsulin to insulin ratio; OGIS insulin sensitivity; QUICKI: fasting insulin sensitivity; GS: β-cell glucose sensitivity; RS: β-cell rate sensitivity; ISRstd: insulin secretion rate at 8 mmol/l glucose; PR: potentiation factor ratio; CLIb: fasting insulin clearance; CLIm: MMTT insulin clearance; HSI: hepatic steatosis index; FLI: fatty liver index; PRS: polygenic risk score; PA: physical activity intensity; SED: sedentary behavior; progr: progression rate; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.



Panel	Threshold on HbA_{1c} progression rate (%/year, mmol mol^{-1} $year^{-1}$)	Number of fast progressors	AUROC [95% CI]	Sensitivity	Specificity	Accuracy
A	0.255, 2.79	33	0.94 [0.87-0.97]	0.84	0.93	0.92
B	0.200, 2.19	61	0.93 [0.88-0.95]	0.86	0.88	0.88
C	0.143, 1.56	110	0.91 [0.87-0.93]	0.87	0.83	0.83
D	0.121, 1.32	131	0.89 [0.85-0.92]	0.81	0.84	0.84

Figure S3. Odds ratios ± 95% confidence interval (CI) from the multivariable logistic analysis of fast *vs* average HbA_{1c} progressors, using different thresholds between the two groups. The independent variables are those identified by multivariable linear analysis of HbA_{1c} progression, excluding MRI variables (N=625). Panels A to D refer to progressively lower thresholds as shown in Figure S1 and in the summary table at the bottom. Age and HDL were log-transformed. Values for sensitivity, specificity and accuracy were derived via maximization of balanced accuracy. OGIS: insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: β-cell glucose sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; RS: β-cell rate sensitivity; BMI: body mass index; progr: progression rate; bas: baseline value; AUROC: area under the receiver operating curve; *: p<0.05; **: p<0.01; ***: p<0.001.